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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/959,160	10/28/97	BALDWIN A	5170.140

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/959,160	Applicant(s) Baldwin et al.
	Examiner Terry A. McKelvey	Group Art Unit 1636

☒ Responsive to communication(s) filed on *10/13/98* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-12* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. (Substitute PTO-948)

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Information Disclosure Statement

The #7 and #8 references in the Information Disclosure Statement filed on 10/2/98 do not comply with the requirements of 37 C.F.R. § 1.98 because the citation data including author, date, etc is missing. This reference has been placed in the application file, but the information referred to therein has not been considered as to the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to a method of enhancing the cytotoxic effects of an antineoplastic chemotherapeutic agent or TNFa, by administering to a subject a therapeutically effective amount of an NF-kB inhibitor in conjunction with the agent of TNFa. The chemotherapeutic agent is limited to daunorubicin, vincristine, and irinotecan in some claims, and, in other claims, the NF-kB inhibitor is limited to various different classes of inhibitors, such as super-repressor IkBa, NF-kB inhibiting proteasome inhibitors, ubiquitin inhibitors, proteasome peptidases, proteases, and antisense oligonucleotides that bind to mRNA encoding NF-kB (a broad range of very different compounds, having very different biochemistries). Thus, the claimed invention is drawn to in vivo therapy comprising administering an antineoplastic chemotherapeutic agent known in the prior art along with an NF-kB inhibitor, few, if any of which have been used in vivo to treat cancer. The only disclosed use for the claimed methods is for treatment of cancer, including any type of cancer from a very large list of cancers set forth in the specification at page 16, paragraph 3.

The nature of the invention is very complex because it is a method to be used to treat cancer, which is a very complex, hard to treat group of diseases. Cancer therapy is well-recognized in the art to be highly unpredictable. See Krontiris which teaches that the various types of cancers have different causative

agents, involve different cellular mechanisms, and, consequently, differ in treatment protocol. Although there exists some treatments for some specific cancers, there are no general treatments taught in the prior art based upon administration of an antineoplastic inhibitor chemotherapeutic agent with a drug chosen because it is an NF-kB inhibitor.

Neither the art nor the specification teaches a working example of administration of an antineoplastic chemotherapeutic agent in conjunction with a specific NF-kB inhibitor to a patient resulting in successful treatment of cancer.

There is no specific guidance in the prior art and only slight, prophetic generic guidance in the specification concerning how to use the claimed method to treat cancer. The

The two basic types of NF-kB inhibitors that the specification addresses: (1) vector or nucleic acid based inhibitors such as gene therapy accomplished by transfecting a cell to be treated with a nucleic acid encoding an NF-kB inhibitor, and transfection of antisense oligonucleotides that inhibit NF-kB RNA; and (2) other compounds that inhibit NF-kB (including both smaller molecules and larger ones such as proteins).

The special considerations with gene therapy are dealt with below. The considerations for the second type of inhibitor also are relevant for gene therapy and antisense therapy.

The specification merely teaches to use an administration method by "any suitable means", as would be apparent to one skilled in the art and briefly mentions some general administration routes and sites that are to be considered for any type of drug administration. General methods of preparing pharmaceutical compositions comprising the two types of drugs to be administered are also taught, along with general possible dosage ranges. The intended patients are taught as being of a very broad class: any humans or animals that suffer from essentially any type of cancer. The specification repeatedly teaches that the particular method used varies depending on the specific agent. However, very significantly, the neither the art nor the specification teaches specific parameters of treatment that have been shown to successfully function for specific NF-kB inhibitors in vivo to treat any disease, let alone cancer. The overall guidance provided is extremely slight because it can be considered to be merely speculative because the effective use of a compound having in vitro biological activity as a drug to treat a disease is extremely unpredictable as taught in the prior art by references such as Caldwell.

Caldwell is cited to show the unpredictability in the art concerning how to make and use a drug. Caldwell teaches that drug action is the result of interaction with target sites, for both desired and undesired actions, modulated by the transfer

processes, the pharmacokinetic variables of absorption, distribution, metabolism and elimination, by which the drug enters and leaves the body. This reference teaches that there is far more inter- and intraspecies variation, in animals and humans, in the factors influencing the nature and extent of internal exposure, than in the sensitivity of drug targets and this pharmacokinetic variability is the cause of major problems in drug development. Caldwell also teaches that failure to take these pharmacokinetic defects, including poor absorption, very short or very long half-life, enzyme induction and high first pass effect, into consideration can cause expensive delay and/or failure during development. This reference thus shows that drug development is very unpredictable, requiring the consideration of many unpredictable factors in determining how to make and use the drug. The specific, very necessary, but unpredictable factors are not taught in either the art or the specification for the claimed administration method for even one combination of chemotherapeutic agent and NF-kB inhibitor, let alone the extremely broad range of combinations encompassed by the claimed invention.

Gibbs et al also teaches that "unfortunately, the translation of modern molecular biology concepts into practical cancer therapeutics has proven to be far more problematic than first anticipated, and few true breakthrough agents have been

found that significantly improve the survival of most cancer patients. A partial explanation for these difficulties lies in understanding the fundamental process of drug discovery and the nature of pharmaceutically useful molecular targets (abstract). This reference also teaches that the existing biological assays are poorly predictive of the clinical efficacy of novel anticancer agents, and that the "take-home" lesson for researchers intent on finding the "cure" for cancer is not that practical intervention is improbable but rather that drug discovery is always difficult (page 197, column 1).

Simply stated, cancer therapy is very empirical. Successful treatments are based upon an extremely large amount of unpredictable trial and error experimentation.

The specification shows that expression of a super-repressor IkBa blocks TNF-stimulated NF-kB nuclear translocation in vitro, enhancing TNF-mediated apoptosis. The specification also shows that proteasome inhibitors enhance TNF apoptosis in vitro, that two types of chemotherapeutic agents, ionizing radiation, and daunorubicin induce nuclear translocation of NF-kB in vitro, and that over expression of the super-repressor enhanced cell killing by the two agents. Finally, the only in vivo data is from an animal model in which an adenoviral vector expressing the super-repressor IkBa is injected into nude mice with experimentally induced fibrosarcomas, along with a cheotherapeutic agent, which

resulted in greater reduction of the tumors compared to the chemotherapeutic agent alone. This data, although it shows that co-administration of the two types of agents for treatment of cancer might have promising biological activity against cancer, it by no means predictably teaches how to predictably use the promising in vitro biological activity (based upon only several different combinations of agents) in an in vivo administration method, as shown by the references described above. The only specific in vivo method taught is based upon one gene therapy method using a nude mice/experimentally induced cancer model. However, nude mice/cancer models are taught by Gura as being very unpredictive for cancer drug discovery. This reference teaches that the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all. It is taught that the animals do not handle the drugs exactly as the human body handles them. This reference specifically teaches that xenograft screening based upon mice with impaired immune systems transplanted with human tumors (the nude mice/tumor model which is the only working example of an in vivo method of the claimed invention taught by the specification, falls into this category) turned out not to be much better than those obtained with the original models, mainly because the xenograft tumors don't behave like naturally occurring tumors in humans. This shows that

results obtained with the in vivo animal model cannot be predictably applied to normal cancer in vivo.

The in vivo model taught in the specification, which is shown by the cited prior art as being very unpredictive for therapy, involves treatment of an organism using in vivo gene therapy. However, the specification fails to adequately teach how to perform gene therapy using the claimed method and vector. Gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See Orkin et al which states (page 1):

"2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host."

The specification generally discloses some of the intended patients, amounts of the vector to be administered, what amount is considered to be therapeutically effective, the route and time course of administration, the sites of administration, the

intended therapeutic product, the intended disease, and the intended target organs. However, this guidance is not significant because it can be considered to be merely speculative because neither the art nor the specification teaches or provides specific guidance to teachings that show that, using the general methods referred to in the specification, a sufficient amount of the NF-kB inhibitor gene can be transferred into cells in vivo and expressed so as to have significant pharmacological effect and that this effect when it occurs in vivo acts to significantly treat cancer. The fact that some general methods referred to in the specification have, with a different gene, been able to get some measure of expression in vivo is in no way predictive that another, unrelated gene like an NF-kB inhibitor gene, can also be expressed to a similar level, and, importantly, be sufficient to treat cancer. There is simply no showing in either the art or the specification that one of skill in the art would be able to use the teachings of the art or the specification to predictably treat cancer using the claimed method in vivo, without much undue experimentation given the nature of the invention and the state of the gene therapy art. Thus, it is not credible, given the consensus scientific opinion concerning the gene therapy art, that one of skill could follow the teachings of the specification and be able to treat cancer using the claimed method without much undue experimentation. The consensus scientific opinion is that

gene therapy was and still is highly unpredictable as evidenced by Orkin et al. The teachings of Verma et al, two years after the Orkin et al publication, reaffirm the teachings of Orkin et al that, even after the two years, there is no evidence of how to use gene therapy to predictably treat any disease (let alone a particular group of diseases, such as cancer as taught by the instant specification). Verma et al teach "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story." (page 239, column 1). This reference teaches the considerable hurdles that must be overcome, including making sure that delivery of the gene gets to the right cells and getting enough of the gene delivered (page 239). This reference teaches that "The Achilles heel of gene therapy is gene delivery ... Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression. Most of these approaches suffer from poor efficiency of delivery and transient expression of the gene." (page 236, column 3). This reference also specifically addresses the problems of adenovirus vectors such as transient expression and considerable immunological problems to be overcome (page 241). Verma et al conclude by stating that "We now need a renewed emphasis on the basic science behind gene therapy-particularly the three intertwined fields of vectors, immunology and cell

biology. ... Clearly, existing vectors need to be streamlined further, and vectors that target specific types of cell are being developed." (page 242).

With regard to use of an antisense molecule against NF-kB in the claimed method, it is equally unpredictable how to use it for cancer therapy, like the other types of inhibitors described above. Also, Branch teaches that they have major, unresolved problems such as: they are far more difficult to produce than was originally imagined, their ability to eliminate the function of a single gene has never been proven, a wide variety of unexpected non-antisense effects occur, making it hard to produce drugs that act primarily through true antisense mechanisms and complicate the use of the agents (abstract; throughout the reference).

In view of the large quantity of experimentation necessary to determine the unpredictable parameters necessary for successfully using a cancer treatment based upon the claimed method in vivo, the lack of significant direction or guidance presented, the absence of working examples, the breadth of the claims which includes the treatment of very many, very different cancers, using a wide range of very different NF-kB inhibitors and chemotherapeutic agent combinations, and the unpredictable and undeveloped state of the art with respect to formulating even one of a broad class of different NF-kB inhibitors into a functional drug that can treat cancer in vivo (along with a

chemotherapeutic agent), let alone a large number of very different inhibitors for various very different cancers, it would require undue experimentation for one skilled in the art to practice the claimed invention.

In conclusion, it has been established by the Court that a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. It is true that a specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. In the instant case, the applicants toss out a mere germ of an idea of how to use a any NF-kB inhibitor, along with an anticancer drug, to treat any cancer, and then essentially simply state that any administration technique known in the prior art as appropriate be used to practice the invention. However, because of the state and

unpredictability of the prior art as evidenced by the cited references, the prior art cannot be relied upon for teachings of specifically how to practice a cancer therapy method based upon a broad class of compounds (NF-kB inhibitors) for which there are no specific teachings taught on how to use the compounds as a therapeutic in vivo. Thus, the specification must teach how to use the invention, a critical detail in teaching the invention. The specification, without working examples or specific guidance to methods that are known to work for the claimed method in vivo, merely relies upon the generic teachings of the prior art as applied to other therapies that cannot be predictably applied to the instant claimed invention. As described above, because of the failure and unpredictability of the prior cancer and gene therapy arts, the prior art cannot be relied upon for enablement of the claimed methods. Therefore, there is no enabling disclosure of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 1, 6, etc, the use of "amount of NF-kB inhibitor" renders the claims vague and indefinite because there is no art recognized "NF-kB inhibitor" and the specification fails to set forth a definition of such. There are NF-kB inhibitors that are known or potentially exist in the art, but none of them are just "NF-kB inhibitor". Amending the claims to insert the proper article in front, e.g., "an NF-kB inhibitor" and using "said NF-kB inhibitor" as appropriate would be remedial.

With regard to claims 1 and 9, the use of "comprising administering ... " renders the claim vague and indefinite because the claim fails to complete the sentence, leaving out to what the administering occurs.

Conclusion

No claims are allowed.

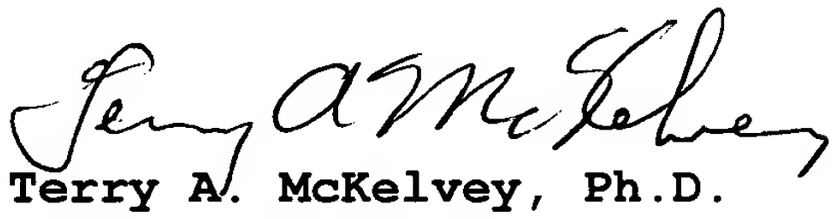
Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December

28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Thursday from about 7:30 AM to about 5:00 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

December 21, 1998